

University of Groningen

## Enantioselective copper-catalysed addition of organometallic reagents using phosphoramidite ligands

Pizzuti, Maria Gabriella

**IMPORTANT NOTE:** You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

*Document Version*

Publisher's PDF, also known as Version of record

*Publication date:*

2008

[Link to publication in University of Groningen/UMCG research database](#)

*Citation for published version (APA):*

Pizzuti, M. G. (2008). *Enantioselective copper-catalysed addition of organometallic reagents using phosphoramidite ligands*. [Thesis fully internal (DIV), University of Groningen]. University of Groningen.

### Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

### Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

**RIJKSUNIVERSITEIT GRONINGEN**

**ENANTIOSELECTIVE COPPER-CATALYSED ADDITION  
OF ORGANOMETALLIC REAGENTS USING  
PHOSPHORAMIDITE LIGANDS**

**Proefschrift**

ter verkrijging van het doctoraat in de  
Wiskunde en Natuurwetenschappen  
aan de Rijksuniversiteit Groningen  
op gezag van de  
Rector Magnificus, dr. F. Zwarts,  
in het openbaar te verdedigen op  
mandag 2 juni 2008  
om 16.15 uur

door

**Maria Gabriella Pizzuti**

geboren op 23 juli 1979  
te Potenza, Italië

Promotores:

Prof. Dr. B. L. Feringa

Prof. Dr. Ir. A. J. Minnaard

Beoordelingscommissie:

Prof. Dr. J. B. F. N. Engberts

Prof. Dr. C. Rosini

Prof. Dr. Ir. H. J. de Vries

ISBN: 978-90-367-3408-0 (printed version)

ISBN: 978-90-367-3443-1 (electronic version)

## Table of contents

### Chapter 1 Introduction

1.1 Conjugate addition reactions	2
1.2 Synthetic applications	3
1.3 Mechanistic studies	19
1.3.1 Dialkylzinc reagents	19
1.3.1.1 Phosphorus ligands	19
1.3.1.2 Non-phosphorus ligands	25
1.3.2 Grignard reagents	28
1.3.3 Trialkylaluminium reagents	34
1.4 Aim and outline of this thesis	35
1.5 References	37

### Chapter 2 Catalytic enantioselective conjugate addition to 2,3-dehydro-4-piperidones

2.1 Introduction	46
2.2 Copper/phosphoramidite catalyzed addition of dialkylzinc reagents to <i>N</i> -protected-2,3-dehydro-4-piperidones	49
2.2.1 Results and discussion	49
2.2.2 Scope of the reaction	53
2.3 Copper/phosphoramidite catalyzed addition of Me <sub>3</sub> Al to <i>N</i> -protected-2,3-dehydro-4-piperidones	55
2.3.1 Literature precedents	56
2.3.2 Results and discussion	58
2.3.3 Co-solvent effect	62
2.4 Further developments	63
2.5 Conclusions	65
2.6 Experimental section	66
2.7 References	77

**Chapter 3 Preparation of trans-2,6-disubstituted-4-piperidones; total synthesis of (+)-myrtine**

3.1 Introduction	82
3.2 Copper-catalyzed conjugate addition to <i>N</i> -protected 4-pyridones	83
3.3 Catalytic enantioselective addition of diethylzinc to <i>N</i> -acyliminium ions	85
3.4 Dehydrogenation of chiral 2-substituted-4-piperidones	89
3.4.1 IBX-mediated dehydrogenation	90
3.4.2 Anodic oxidation of carbamates	91
3.5 $\alpha$ -Lithiation of Boc protected amines	93
3.6 Synthesis of (+)-myrtine	100
3.7 Conclusions	102
3.8 Experimental section	103
3.9 References	113

**Chapter 4 Catalytic enantioselective addition of organometallic reagents to *N*-formylimines using monodentate phosphoramidite ligands**

4.1 Introduction	118
4.2 State of the art in the addition of organozinc reagents to imines	120
4.3 Copper-catalyzed addition of organozinc reagents using phosphoramidite ligands	124
4.3.1 Optimization of the reaction conditions	124
4.3.2 Organometallic reagent scope	127
4.3.3 Substrate scope	131
4.4 Studies on <i>in situ</i> ligand oxidation	135
4.4.1 Synthesis of the phosphoric amide ( <i>S,R,R</i> )- <b>L2</b>	138
4.4.2 Ligand oxidation	140
4.5 Conclusions	145
4.6 Experimental section	148
4.7 References	167

**Chapter 5 Catalytic enantioselective addition of organozinc reagents to *N*-acyloxyiminium ions**

5.1 Introduction	174
5.2 Results and discussion	177
5.2.1 From N-oxides to <i>N</i> -acyloxyiminium ions	177
5.2.2 Enantioselective addition to N-oxide via <i>N</i> -acyloxyiminium ions	180
5.2.3 Scope of organozinc reagents	188
5.3 Conclusions	189
5.4 Experimental section	190
5.5 References	197

**Chapter 6 Copper-catalyzed enantioselective conjugate addition of organometallic reagents to acyclic dienones**

6.1 Introduction	202
6.1.1 Enantioselective copper-catalyzed conjugate addition of organozinc reagents to acyclic substrates	202
6.1.2 Enantioselective copper catalyzed conjugate addition of organozinc and organoaluminum reagents to cyclic dienones	208
6.2 Copper-catalyzed enantioselective conjugate addition of organozinc reagents and trimethylaluminium to acyclic dienones	212
6.2.1 Sequential conjugate addition	217
6.2.2 Tandem conjugate addition	217
6.3 Conclusions	219
6.4 Experimental section	220
6.5 References	229

<b>Samenvatting</b>	233
---------------------	-----

<b>Discussione generale</b>	238
-----------------------------	-----

<b>Acknowledgment</b>	241
-----------------------	-----

